

Attorney Docket No. 9448-16CT2  
In re: Hill et al.  
Serial No.: 10/628,057  
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### REMARKS

Applicants appreciate the thorough examination of the present application as evidenced by the final Office Action dated August 16, 2005 (hereinafter, "the Final Action"). Claims 1, 4-7, 10, 13-18, 21, 24-29 and 32-36 stand rejected. Claims 1, 4-7, 10, 13-18, 21, 24-29 and 32-34 are pending upon entry of the present Amendment. Applicants respectfully submit that Claims 1, 4-7, 10, 13-18, 21, 24-29 and 32-34 are patentable and that the present application is in condition for allowance for at least the reasons discussed below.

#### I. Double Patenting

Applicants appreciate the Examiner's acknowledgement that the obviousness-type double patenting rejection of the claims over various issued claims of U.S. Patent Nos. 6,844,334; 6,660,726; and 6,855,703 is now moot in view of the filing of a terminal disclaimer.

#### II. Claim Objections Under 37 C.F.R. §1.75

The Final Action maintains the objection to Claims 35 and 36 as being a substantial duplicate of Claims 33 and 34, respectively. *See* Final Action, page 2. Applicants have canceled Claims 35 and 36 thereby obviating this objection. Accordingly, Applicants respectfully request that this objection be withdrawn.

#### III. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Applicants appreciate the indication that the rejection of Claims 18 and 29 under 35 U.S.C. § 112, first paragraph, has been withdrawn. However, the rejection of Claims 33-36 has been maintained. More specifically, the Final Action asserts that "[t]he disclosure of glucoronides or the specific peaks in the specification does not provide support for the specific compounds as recited in the instant claims because there is no correlation between said disclosure(s) and said compounds. . . . It is also noted that parent case identifies identical peaks for compounds having different substituents in the 3-position and, thus, said peaks are not specific for the claimed compounds or the group attached to the 3-position of the instantly claimed compounds." Final Action, page 4 (citations omitted). Applicants respectfully disagree.

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The specification recites "glucuronide"<sup>1</sup> as a potential substituent for the formula of the compounds disclosed in the present application. *See* Present Application, page 3, lines 1-4 and page 7, lines 16-2, among other places.  $\text{NaC}_6\text{H}_8\text{O}_7$ , which is recited in Claims 33 and 34, is a non-limiting example of a glucuronide present in embodiments of the present invention. The nuclear magnetic resonance (NMR), in particular,  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR, spectrum peaks further provide support for the recited claims. As recognized by one skilled in the art, it is possible for different substituents to have the same or similar chemical shifts while maintaining the accuracy of NMR spectroscopy in providing specific information regarding the molecular structure of a compound. Thus, one skilled in the art would not be misguided by the observation that parent case identifies identical peaks for compounds having different substituents in the 3-position. Instead, it is the combination of the chemical formula and spectral characteristics providing the physicochemical characteristics of the compound that enable the skilled artisan to arrive at the specific compounds recited in the pending claims. This disclosure providing the tools for the skilled artisan to arrive at the specific compounds can be found in the specification including the drawings, i.e., spectra presented therein.

Applicants have canceled Claims 35 and 36, and thus, in view of the foregoing, Applicants respectfully submit that Claims 33 and 34 are supported by the present specification, and Applicants respectfully request that claim rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

#### IV. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Applicants appreciate the indication that the rejection of Claims 5, 14 and 25 under 35 U.S.C. § 112, second paragraph, has been withdrawn. However, the rejection of Claims 1, 4, 6, 7, 10, 13, 15-18, 21, 24, 26-29 and 32 has been maintained. The Final Action maintains the rejection stated in the Office Action dated February 22, 2005 indicating that it is unclear how a substituent of  $\text{R}_4$ - $\text{R}_7$  and  $\text{R}_{10}$ - $\text{R}_{13}$  can represent ketone when the other substituent at the same position represents another atom such as hydrogen. *See* Office Action dated February 22, 2005, page 6.

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<sup>1</sup> The spelling of "glucoronide" has been corrected to reflect "glucuronide" in the amendments to the specification and claims presented herein. As this is a correction of a typographical error, Applicants respectfully submit that no new matter is added by way of these amendments.

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Applicants have previously submitted that it is at this position where a ketone is formed, not at the site where the carbon that the R<sub>4</sub>-R<sub>7</sub> or R<sub>10</sub>-R<sub>13</sub> is attached. Applicants further submit that substituents R<sub>4</sub>-R<sub>7</sub> and R<sub>10</sub>-R<sub>13</sub> can represent ketone when the substituent is one that includes a ketone group. Alternatively, when the substituent does not include a ketone group, the substituent is selected from one of the other substituents recited in the claim, for example, hydrogen, hydroxyl, lower alkyl, lower alkoxy, halogen or a carbonyl group as recited in Claim 1. Thus, Applicants respectfully submit that one skilled in the art would be apprised of the chemical structure of the compound in view of the claim recitations and general knowledge of chemical concepts.

Accordingly, Applicants respectfully submit that Claims 1, 4, 6, 7, 10, 13, 15-18, 21, 24, 26-29 and 32 are not indefinite, and Applicants respectfully request that the claim rejections under 35 U.S.C. §112, second paragraph, be withdrawn. Should the Examiner find the above remarks pertaining to this rejection unpersuasive, Applicants respectfully request that the Examiner contact the Applicants' representative so that Applicants may fully understand and address the Examiner's concern.

#### V. Other Matters

Applicants have amended the title to delete the recitation "Novel" as requested by the Examiner.

#### VI. Claim Rejections Under 35 U.S.C. § 102

The Final Action maintains the rejection of Claims 1, 4-7, 10, 13-16, 21, 24-27 under 35 U.S.C. § 102(b) as being anticipated by IL 25265 to Harnik (hereinafter, "Harnik"). More specifically, the Final Action states that "[t]he claimed compounds include conjugates thereof and, thus, the skilled artisan in the art would consider the compounds taught by Harnik to be conjugates of the claimed compounds. The examiner notes the definition of 'conjugates' set forth in the present specification (see page 8, lines 10-12) and the level of skill of the ordinary artisan in the art at the time of the present invention." Final Action, page 5. Applicants respectfully disagree.

Applicants reiterate that Harnik merely discusses synthesis of particular estrogenic estrane derivatives. These derivatives and the reaction products described in the synthesis do

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not teach or suggest a substitution at the 3 position to provide the compounds recited in the pending claims. In particular, independent Claims 1 and 10 recite "R<sub>3</sub> is hydrogen, sulfate, glucuronide or a conjugate thereof." Harnik, however, discusses compounds having a methoxy group at the 3 position of a 1,3,5,6,8 estrapentaene backbone. Harnik neither teaches nor suggests the claimed compounds having the recited substituents at the 3 position. Further, in contrast to the assertions of the Final Action, the skilled artisan would not consider the compounds discussed by Harnik to be "conjugates of the 'claimed compounds.'" The language provided in the specification regarding "conjugates" recites as follows:

Compounds of the present invention may be present in a conjugated form. The conjugates may be various conjugates understood by those skilled in the art, including, but not limited to, glucuronide and sulfate. The most preferred conjugate is sulfate.

Where Harnik fails to discuss compounds having hydrogen, sulfate, glucuronide or a conjugate thereof at the 3 position and discusses only a methoxy group at this position, the skilled artisan would not consider Harnik to teach or suggest conjugates of the "claimed compounds."

Further, Applicants reiterate that case law holds and the Manual of Patent Examining Procedure (MPEP) states that a claim is anticipated only if each and every recitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The Final Action states that "the ordinary artisan in the art would expect that the compound(s) would be in pure form." Final Action, page 6. For at least the reasons discussed above, Harnik fails to teach or suggest the claimed compounds. Harnik also fails to teach or suggest that the compounds provided in Harnik are in pure form. As noted above, Harnik provides the synthesis for particular estrogenic estrane derivatives. The synthesis scheme does not teach or suggest methods for deriving purified compounds. Absent this teaching or suggestion, Applicants respectfully submit that one skilled in the art would expect that the compounds exist in the form discussed in the reference and nothing more. In this instance, the reference does not indicate that the compounds exist in a pure form.

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Accordingly, Harnik does not teach or suggest the claimed compounds and further does not teach or suggest the claimed compounds in a pure form.

As previously noted, Harnik discusses synthesis of estrogenic estrane derivatives. Applicants respectfully submit that Harnik does not teach or suggest "a pharmaceutical composition incorporating a compound represented by Formula I" as recited in Claim 10, or "a method of treating a subject in need of estrogen therapy, said method comprising administering an effective amount of a compound represented by Formula I . . . said compound being present in pure form" as recited in Claim 21. "Anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every recitation of a claimed invention." *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000) (relying on *Electro Med. Sys. S.A. v. Cooper Life Scis.*, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994)). The proposed synthetic scheme for particular estrogenic estrane derivatives does not teach or suggest a pharmaceutical composition or a method of treating a subject in need of estrogen therapy.

Lastly, a compound or composition of matter is anticipated if the disclosure in a single reference places that compound or composition in possession of the public. See *In re Brown*, 329 F.2d 1006, 141 USPQ 245 (CCPA 1964). Thus, it is well accepted that the reference must therefore provide a certain degree of precision with respect to the specific compound claimed. Clearly, Harnik does not provide that degree of precision where Harnik fails to teach or suggest the specific substitutions, pharmaceutical compositions, methods of treatment and chemical purity associated with the compounds of the present invention.

Accordingly, Applicants respectfully submit that Harnik does not anticipate Claims 1, 4-7, 10, 13-16, 21 and 24-27, and Applicants respectfully request that these claim rejections be withdrawn.

#### **VII. Claim Rejections Under 35 U.S.C. § 103**

The Final Action maintains the rejections of Claims 17-18 and 28-29 and 32 under 35 U.S.C. § 103(a) as being obvious in view of Harnik. The Final Action states that "it is well known in the art to utilize estrogenic compounds for estrogenic replacement therapy. Thus, the use of prior art estrogenic compounds for estrogen replacement therapy would be obvious to the skilled artisan in the art." Final Action, page 6. Applicants respectfully disagree.

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Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. In particular, in order to establish a *prima facie* case of obvious, three basic criteria must be met:

- (1) The cited reference or combination of references must teach or suggest all the claim recitations. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970);
- (2) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker*, 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986); and
- (3) There must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

For at least the reasons discussed above, Applicants respectfully submit that Harnik fails to teach or suggest the compounds recited in Claims 10 and 21. Thus, the first criterion has not been met.

For reasons previously made of record, Applicants do not agree that one of ordinary skill in the art would be motivated to use the compounds discussed in Harnik or those recited in the pending claims for estrogen replacement therapy, absent the teachings of the present application. At best, one of ordinary skill in the art may find it obvious to *try* the compounds discussed in Harnik in estrogen replacement therapy. "Obvious to try," however, is not the standard for establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. The Federal Circuit has held that in evaluating obviousness, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In terms of the expectation of success of using the compounds discussed in Harnik, Applicants respectfully submit that one of ordinary skill in the art would not have a reasonable expectation of success of using the compounds discussed in Harnik as (a) a pharmaceutical composition in combination with at least one additional pharmaceutically active ingredient, or (b) in a method of treating subjects in need of estrogen therapy. Harnik fails to teach or suggest that the compounds discussed therein could be used for estrogen therapy or that the compounds in combination with the at least one additional pharmaceutically active ingredient would maintain any estrogenic properties, if any were initially present, and be useful in

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treatment of hypo-estrogenic conditions known in the art such as those associated with menopause. Thus, neither the second nor third criterion have been met.

Accordingly, Applicants respectfully submit that Claims 17-18 and 28-29 and 32 are not obvious in view of Harnik, and Applicants respectfully request that these claim rejections be withdrawn.

### CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is believed that no other fees and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully Submitted,



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### CERTIFICATION OF FACSIMILE TRANSMISSION UNDER 37 CFR § 1.8

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office via facsimile number 571-273-8300 on November 16, 2005.



Susan E. Freedman

Date of Signature: November 16, 2005